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Blood Pressure Targets for Adults with Vasodilatory Shock — An Individual Patient Data Meta-Analysis

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Abstract

BACKGROUND We sought to estimate whether a lower mean arterial blood pressure target, compared with a higher mean arterial blood pressure target, reduced 90-day all-cause mortality among critically ill adult patients with vasodilatory shock.

METHODS We conducted an individual patient data meta-analysis of randomized controlled trials that evaluated the effect of distinct thresholds of mean arterial blood pressure to guide vasopressor support among critically ill adults identified in a systematic literature search. The main exposure was a lower mean arterial pressure target compared with a higher mean arterial pressure target (including usual care). The primary outcome was 90-day all-cause mortality. We used a Bayesian random effects log-binomial model to estimate risk ratios with 95% credible intervals (CrIs).

RESULTS Between 2010 and 2019, 3352 patients were randomly assigned in three trials (SEPSISPAM, OVATION pilot trial, and 65-Trial) across 103 hospitals from the United Kingdom, France, and Canada. When compared with a higher mean arterial blood pressure target or usual care, the risk ratio for 90-day all-cause mortality associated with a lower blood pressure target was 0.93 (95% global: CrI, 0.76 to 1.07; low certainty, posterior probability of benefit 87%). Results were consistent across multiple secondary and sensitivity analyses, including adjustment for prognostically important baseline covariates and alternative modeling techniques. Multiple approaches to evaluate the heterogeneity of treatment effect did not identify any subgroups that may potentially benefit from higher mean arterial blood pressure targets.

CONCLUSIONS Targeting a lower mean arterial blood pressure for vasopressor therapy in critically ill patients with vasodilatory shock possibly reduced 90-day all-cause mortality. However, the certainty of evidence is low, and this analysis does not exclude the possibility that lower targets may cause harm overall.

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Introduction

Blood pressure targets — generally using mean arterial blood pressure — to guide the use and dose of vasopressor support for critically ill adult patients with shock remain variable.[1-3] Vasopressors to achieve such targets are one of the most widely used life support interventions among critically ill adults. However, there is an inherent tension between aiming to maintain adequate perfusion pressure with vasopressors and the potential associated risks of vasoconstriction and other effects (e.g., chronotropy, inotropy).[4] Therefore, three randomized controlled trials have evaluated the effect of distinct thresholds of mean arterial blood pressure to guide vasopressor support among critically ill adults, with indeterminate results.[5-7]

Despite current guidelines recommending a target mean arterial blood pressure of 65 mmHg over higher targets for adult patients with septic shock,[8] clinicians frequently aim for higher values, usually on the basis of individual patient characteristics such as age or the presence of comorbidities (e.g., hypertension).[4,9] In the face of the underlying uncertainty, as when the null hypothesis is not rejected, a Bayesian approach may complement a frequentist framework.[10-12] For example, by incorporating prior knowledge and estimating posterior probabilities of benefit and harm, a Bayesian analysis may protect against an overly conservative interpretation of a null result that may lead clinicians to ignore or abandon potentially beneficial treatments.[11] When interventions are used very frequently or when the baseline risk of death is high — both conditions apply to vasopressors — even small relative effects may have a large impact at the population level.[13,14] In addition, complementary Bayesian analyses of individual patient data may identify potential sources of heterogeneity hidden in the average treatment effects estimated in clinical trials.[15]

Considering the overall imprecision of estimates in individual trials, the potential for unrecognized heterogeneity of treatment effects, and the potential for harm of a widely used intervention, we undertook a Bayesian individual patient data meta-analysis of three randomized controlled trials to investigate whether a lower mean arterial blood pressure target, compared with a higher mean arterial blood pressure target (including usual care), reduced 90-day all-cause mortality among adult critically ill patients with vasodilatory shock.

Methods

STUDY DESIGN

We conducted a Bayesian meta-analysis of individual patient data collected in three randomized controlled trials previously included in a recently published systematic review and study-level meta-analysis, which also reported the full literature search strategy.[16] Each trial evaluated different mean arterial blood pressure targets for vasopressor therapy in critically ill adults with vasodilatory shock. Specifically, the SEPSISPAM trial compared a lower target mean arterial pressure of 65 to 70 mmHg with a higher target mean arterial pressure of 80 to 85 mmHg (focused on patients with sepsis)[7]; the OVATION pilot trial compared a lower target of 60 to 65 mmHg with a higher target of 75 to 80 mmHg[6]; and the 65-Trial compared a lower target of 60 to 65 mmHg with usual care as per the treating clinician (median mean arterial pressure in the comparator group, 73 mmHg).[5] Protocols and results of the three original trials have been reported elsewhere[5-7]; main characteristics are summarized in Table S1 in the Supplementary Appendix. The lead investigators agreed to assemble deidentified individual patient data from the three trials into a single database to conduct prespecified analyses. Our statistical plan has been registered in advance and can be found elsewhere.[17] Before pooling data, we compared trial protocols, case report forms, and data dictionaries to create a unified data mapping ontology.

EXPOSURE AND OUTCOMES OF INTEREST

Our main exposure of interest was a lower mean arterial blood pressure target (as defined in individual trials) compared with a higher mean arterial blood pressure target or usual care (as defined in individual trials; this also included unprotocolized usual care in the 65-Trial). The primary outcome was 90-day all-cause mortality. Notably, this was the primary outcome in the 65-Trial and a secondary outcome in the SEPSISPAM trial. In the OVATION pilot trial, 90-day mortality was not a prespecified outcome, but these data were recorded and made available by the trial investigators. Our causal contrast of interest was the intention-to-treat effect.[18]

RISK OF BIAS ASSESSMENT AND GRADING OF THE EVIDENCE

Risk of bias assessment has been performed and reported previously, using the Cochrane risk of bias 2.0 tool.[16] We rated the certainty of evidence using the Grading

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of Recommendations Assessment, Development, and Evaluation (GRADE) system.[19] We assessed imprecision using a 1 percentage point absolute difference in 90-day mortality as the threshold for a minimally important difference.[16] We describe the certainty of evidence using GRADE guidelines.[20]

MAIN STATISTICAL ANALYSIS

We used descriptive statistics to summarize baseline characteristics of participants. We captured information on age, sex, chronic hypertension, chronic heart failure, coronary artery disease, and chronic kidney disease; and characteristics of the hospital stay at the time the patient was randomly assigned to a trial group, including the Acute Physiology and Chronic Health Evaluation II (APACHE II) score,[21] sepsis, and the receipt of renal replacement therapy. Notably, patient data from the SEPSISPAM trial did not include APACHE II scores, either at baseline or after trial inclusion.[7] The APACHE II score for these patients was estimated based on a Poisson regression model that was trained in the 65-Trial and the OVATION pilot trial. We assessed the balance of baseline characteristics with standardized mean differences.[22]

To estimate the effect of a lower mean arterial blood pressure target (compared with a higher mean arterial blood pressure target) on 90-day all-cause mortality, we fitted a one-stage random-effects Bayesian log-binomial model with a weakly informative prior for the treatment effect.[23] This model included a random intercept for trial and a random treatment effect; we utilized a random treatment effect due to differences in mean arterial blood pressure targets across trials. We report results as a median risk ratio with 95% percentile-based credible interval (CrI). We also present absolute risk differences (assuming a 40% baseline risk of 90-day mortality in the comparator group),[5] and posterior probabilities of any benefit (i.e., risk ratio <1.0). Further details on modeling and statistical analysis can be found in the Supplementary Appendix. We used a complete-case approach for our main analyses.

ADDITIONAL ANALYSES

We performed several secondary analyses and sensitivity analyses to assess the robustness of our main analysis. First, since different practitioners may have different prior beliefs, we refitted our main analysis using optimistic, skeptical, and pessimistic priors; see details on prior specification in the Supplementary Appendix. Second, to assess the impact of our modeling choices, we reestimated our results using Bayesian log-binomial models with four different effects: with random effects for trial but only fixed effects for treatment allocation, with random effects for site but only fixed effects for treatment allocation, with random effects for trial and site, and using a strong pessimistic prior. Third, we presented estimates adjusted for baseline characteristics (i.e., age, sex, comorbidities, and severity of disease); the subset of covariates was chosen a priori to represent a minimal set of important predictors of the outcome of interest (original adjustment in secondary analysis in individual trials is presented in Table S1).[24] Fourth, since SEPSISPAM evaluated higher blood pressure targets than the other two trials, and the 65-Trial used unprotocolized usual care as a comparator, we restricted our analysis to results from either the 65-Trial and OVATION trials or the SEPSISPAM and OVATION trials. Fifth, since there was missing information for some prognostically important covariates used in our adjusted model, we performed multiple imputation using chained equations in a post hoc analysis.[25] Finally, since estimates from a one-stage meta-analytic approach may differ from a two-stage approach, we also included ad hoc analyses of Bayesian random or fixed effects models fitted using a two-stage approach.[26]

HETEROGENEITY OF TREATMENT EFFECT

With the intention of informing the design of future trials, we explored potential heterogeneity of treatment effect using several approaches: conventional single-variable subgroup analyses, a risk-based approach using the APACHE II score, a risk-based approach using Bayesian additive regression trees, and a clustering approach using latent class analysis.[15] No multiplicity adjustments for subgroup analysis were defined; credible intervals should not be used to infer definitive effects.

Single-variable subgroup analyses were prespecified[16] and included age (patients younger than 65 years of age vs. patients older than 65 years of age, hypothesizing that lower vasopressor exposure would be more beneficial in older patients); presence of hypertension (yes vs. no, hypothesizing that patients with hypertension would benefit more from higher vasopressor exposure); presence of chronic heart failure (yes vs. no, hypothesizing that lower vasopressor exposure would be more beneficial among patients with heart failure); chronic kidney disease (yes vs. no, hypothesizing that patients with chronic kidney disease would benefit more from higher vasopressor exposure); presence of sepsis (yes vs. no, hypothesizing that lower vasopressor exposure would be more beneficial among patients with sepsis); and the APACHE II score (original scale 0 to 71 points, with more points indicating increased

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severity, categorized as >21 vs. ≤21 points, hypothesizing that lower vasopressor exposure would be more beneficial among more severely ill patients). For each subgroup analysis, interaction terms between treatment allocation and subgroup indicators were included. Both trial-level mean values and their interaction with treatment assignment (i.e., modeling between-trial variation) were also included to avoid aggregation bias across all analyses.[27] We report estimated effects in each subgroup as risk ratio with 95% CrI, along with posterior probabilities of interaction, as the probability that the risk ratio in one subgroup is larger than in the other, with directionality defined as above.[15] We used the Instrument for assessing the Credibility of Effect Modification Analyses (ICEMAN) and adapted the P value criteria to posterior probabilities (i.e., presence of heterogeneity defined as a posterior probability of interaction in the prespecified direction equal or larger than 99%).[28]

To inform the design of future trials, we also conducted several exploratory analyses. These included using an unsupervised learning approach to detect distinct clusters of critically ill patients with hypotension. A latent class analysis including only clinical variables available at the time the patient was randomly assigned (i.e., age, sex, comorbidities, severity as measured by the APACHE II score, presence of sepsis, and receipt of renal replacement therapy) was fitted by maximizing the likelihood function, and the optimal number of clusters decided by the lowest Bayesian information criterion.[29] Finally, we explored the presence of heterogeneity by baseline risk[30] modeled as quantiles using either the APACHE II score or fitted probabilities from Bayesian additive regression trees.[31] For these models, we explored the presence of heterogeneity of treatment effect in a similar way to previous analyses (see above).

We used R version 4.1.0 (R Foundation for Statistical Computing) for dataset generation, description, and analysis (using rstanarm for all Bayesian models).

Results

STUDY PATIENTS

Between 2010 and 2019, 3352 patients were randomly assigned in the three trials across 103 hospitals from United Kingdom, France, and Canada (Fig. 1). No hospital recruited patients in more than one trial. Baseline characteristics are presented in Table 1. Overall, mean age was 72 years of age, more than half of patients were male (59%), and the most common comorbidity was hypertension

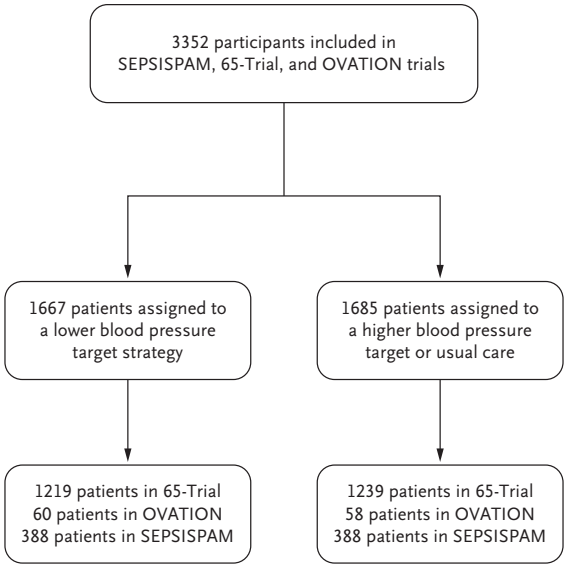
3352 participants included in SEPSISPAM, 65-Trial, and OVATION trials
1667 patients assigned to a lower blood pressure target strategy
1685 patients assigned to a higher blood pressure target or usual care
1219 patients in 65-Trial
60 patients in OVATION
388 patients in SEPSISPAM
1239 patients in 65-Trial
58 patients in OVATION
388 patients in SEPSISPAM

Figure 1. Patient Participation in the SEPSISPAM, 65-Trial, and OVATION trials.

(51%) followed by coronary artery disease (13%). The median APACHE II score on admission was 21 points, and most patients had sepsis as the mechanism for their vasodilatory shock (76%). Characteristics were balanced at the time patients were randomly assigned (Table 1). The average mean arterial blood pressure and cumulative vasopressor dose by group and trial are shown in Figure S1. Treatment estimates in individual trials while performing Bayesian reanalysis with weakly informative priors are presented in Table S2.

PRIMARY OUTCOME

The estimated effects of a lower mean arterial blood pressure target for vasopressor use (compared with a higher target) on 90-day all-cause mortality are summarized in Table 2. In the primary analysis, when compared with a higher mean arterial blood pressure target, a lower mean arterial blood pressure target was associated with a 7% relative reduction in the risk of all-cause mortality at 90 days (risk ratio, 0.93; 95% CrI, 0.76 to 1.07; low certainty). The posterior probability of benefit using a lower mean arterial blood pressure target was 87% and the corresponding estimated absolute risk difference was −2.6 percentage points (95% CrI, −9.6 to 2.8).

ADDITIONAL ANALYSES

The use of a lower mean arterial blood pressure target was also associated with a reduction in the risk of 90-day

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Table 1. Baseline Characteristics of Study Participants.*

Baseline Characteristic†	Lower Mean Arterial Blood Pressure Target (n=1667)	Higher Mean Arterial Blood Pressure Target (n=1685)	SMD
Demographics and comorbidities			
Age, years — mean (SD)	72.6 (10.3)	72.4 (10.2)	0.02
Female sex — %	41.3	41.2	0.00
Coronary artery disease — %	13.4	13.5	0.00
Hypertension — %	51.9	50.6	0.03
Congestive heart failure — %	11.5	11.9	0.01
Chronic kidney disease — %	2.2	2.0	0.01
Severity of disease			
APACHE II score, points — median (IQR)‡	21 (17 to 26)	21 (17 to 26)	0.05
Sepsis at admission — %	75.6	76.3	0.02
Renal replacement therapy — %	10.6	9.8	0.03
Trial enrollment — %			
65-Trial	73.1	73.5	0.01
OVATION	3.6	3.4	—
SEPSISPAM	23.3	23.0	—

* APACHE II denotes Acute Physiology and Chronic Health Evaluation II; IQR, interquartile range; SD, standard deviation; and SMD, standardized mean difference.

† Hypertension data missing for 11.6% of patients; chronic kidney disease data missing for 0.5% of patients; renal replacement therapy data missing for 0.5% of patients; APACHE II scores missing for 0.3% of patients (after imputation for those patients in SEPSISPAM); sex data missing for 0.08% of patients; and age data missing for 0.03% of patients.

‡ The APACHE II score was not available for patients included in the SEPSISPAM trial and was derived using a Poisson regression model that was trained in the 65-Trial and OVATION pilot study subset. The main predictor was the probability of all-cause mortality (as quantified by the Simplified Acute Physiology Score in SEPSISPAM). (APACHE II score range, 0 to 71 points, with more points indicating increased severity).

all-cause mortality under a variety of sensitivity analyses, including the use of varying prior beliefs including strong pessimistic priors, fixed effects models, removing data from either SEPSISPAM or the 65-Trial, after adjusting for prespecified baseline variables, and using multiple imputation with chained equations to account for missing covariate data (Table S3). Our estimates were also consistent while performing two-stage fixed or random effects meta-analysis (Table S2). Certainty assessment for the primary analysis is presented in Table S4.

HETEROGENEITY OF TREATMENT EFFECT

The main estimated effects were consistent across different prespecified subgroups of interest (Fig. 2 and Table S5). No clinically meaningful differences were found, with all posterior probabilities of an interaction between the intervention and the subgroup-defining variables consistently below 99%. Notably, no point estimate favored a higher target for mean arterial blood pressure. Credibility of effect measure modification using ICEMAN is shown in Table S5.

Using clinical variables, we found two distinct clusters of patients at baseline (Table S6). Overall, patients in cluster 2 had a higher baseline burden of comorbidity (including hypertension and chronic kidney disease), higher severity of illness at baseline, and a higher proportion receiving baseline renal replacement therapy. However, there was no evidence of heterogeneity of treatment effect introduced by clustering (Table S6). Similar results were obtained when using a risk-based approach with either baseline APACHE II scores or Bayesian additive regression trees (Table S6).

Discussion

Our results suggest that, in general, targeting a lower mean arterial blood pressure for vasopressor therapy in critically ill adults with vasodilatory shock possibly reduced all-cause mortality at 90 days. However, important uncertainty in estimates remains. At present, using available clinical trial evidence, the potential survival benefit (if any) appears to be similar and small across all evaluated clinical subgroups. Because vasopressors are administered to critically ill patients globally, this small survival benefit, if true, would be meaningful. Alternatively, if higher and lower blood pressure targets are equivalent with respect to mortality (i.e., risk ratio ~1.0), a default of using lower blood pressure

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Table 2. Effect of a Lower Mean Arterial Blood Pressure Target on All-Cause Mortality at 90 Days in Critically Ill Adult Patients with Vasodilatory Shock.*

Analysis	Risk Ratio (95% CrI)	RD (95% CrI)	Probability Risk Ratio <1.0
Primary analysis			
Random effects model; weakly informative prior belief	0.93 (0.76 to 1.07)	−2.6 (−9.6 to 2.8)	87%
Two-stage approach for meta-analysis			
Random effects model; weakly informative prior belief	0.93 (0.76 to 1.09)	−2.8 (−9.6 to 3.6)	82%
Fixed effects model; weakly informative prior belief	0.93 (0.86 to 1.01)	−2.8 (−5.6 to 0.4)	96%
Treatment estimates under different priors			
Random effects model; prior belief ∼ lower target better†	0.93 (0.77 to 1.07)	−2.8 (−9.2 to 2.8)	89%
Random effects model; skeptical prior belief‡	0.94 (0.81 to 1.07)	−2.5 (−7.8 to 2.8)	87%
Random effects model; prior belief ∼ higher target better§	0.94 (0.81 to 1.12)	−2.4 (−7.4 to 4.9)	86%
Random effects model; strong prior belief ∼ higher target better¶	0.95 (0.85 to 1.12)	−1.8 (−6.1 to 5.0)	79%
Alternative modeling techniques			
Fixed effect for treatment, random effects for study	0.93 (0.87 to 1.02)	−2.8 (−5.2 to 0.8)	94%
Fixed effects for treatment, random effects for study and site	0.94 (0.87 to 1.01)	−2.4 (−5.4 to 0.4)	95%
Fixed effects for treatment, random effects for site	0.94 (0.87 to 1.01)	−2.4 (−5.4 to 0.6)	95%
With restriction or adjustment			
Excluding patients from SEPSISPAM trial	0.92 (0.54 to 1.57)	−3.3 (−18.5 to 22.8)	79%
Excluding patients from 65-Trial	0.93 (0.46 to 1.52)	−3.0 (−21.5 to 20.7)	71%
Multivariable adjustment for APACHE II score	0.90 (0.62 to 1.20)	−4.0 (−15.0 to 8.4)	84%
Multivariable adjustment for age, sex, comorbidities, and severity of illness‖	0.93 (0.78 to 1.15)	−2.7 (−8.9 to 6.0)	82%

* Results with a risk ratio of less than 1.0 and risk difference of less than favor the lower mean arterial blood pressure target. The main analysis employed a random effects model with random intercepts for trial. Probabilities of any benefit (i.e., risk ratio <1.0 or RD<0) are equivalent since they are based on the same model (using a predefined baseline risk for RD calculation). APACHE II denotes Acute Physiology and Chronic Health Evaluation II; CrI, credible interval; and RD, risk difference.
† Optimistic prior ∼N (−0.2, 0.4).
‡ Skeptical prior ∼N (0, 0.35).
§ Pessimistic prior ∼N (0.2, 0.4).
¶ Strong pessimistic prior ∼N (0.2, 0.2).
‖ Multivariable adjustment included the following variables measured at or prior to the time patients were randomly assigned a treatment group: age, sex, comorbidities (i.e., hypertension, congestive heart failure, chronic kidney disease, coronary artery disease), renal replacement therapy, and sepsis. We used a complete-case analysis.

targets could avoid the disadvantages associated with more intensive vasopressor therapy.

Our results raise concerns because contemporaneous data suggest that usual care practices expose patients to higher doses of vasopressors than may generally be warranted; for example, patients randomly assigned to usual care in the 65-Trial had mean arterial blood pressure values of 72 mmHg while receiving vasopressors.[5] In a single-center observational study of vasopressor use, average mean arterial pressure values during vasopressor therapy were above the 65 mmHg target.[32] Clinicians may therefore have a heightened concern regarding the potential deleterious effects of hypotension on mortality on the basis of observational studies.[33,34] If the estimates from our analysis are accurate, the majority of critically ill adult patients with vasodilatory shock may be treated in a way that may increase their risk of 90-day all-cause mortality.

Another plausible source of opposition to the use of permissive hypotension is the belief that the optimal dosing strategy for vasopressors varies across different subgroups.[35,36] Although our analysis did not find any credible subgroup effect, such an effect remains possible because the volume of information required to refute subgroup effects considerably exceeds currently available clinical trial data. A large global trial collaboration with detailed, high-quality data would be required to ascertain the average effect and any heterogeneity of treatment effect for this intervention. Reducing residual uncertainty will also require clinicians to move beyond binary data interpretation[37] and an ethics framework that facilitates efficient trial conduct by mitigating the harm of "research hyper-regulation" for this routine therapy for critically ill patients with shock.[38] In the interim, there is a discrepancy between default usual practices

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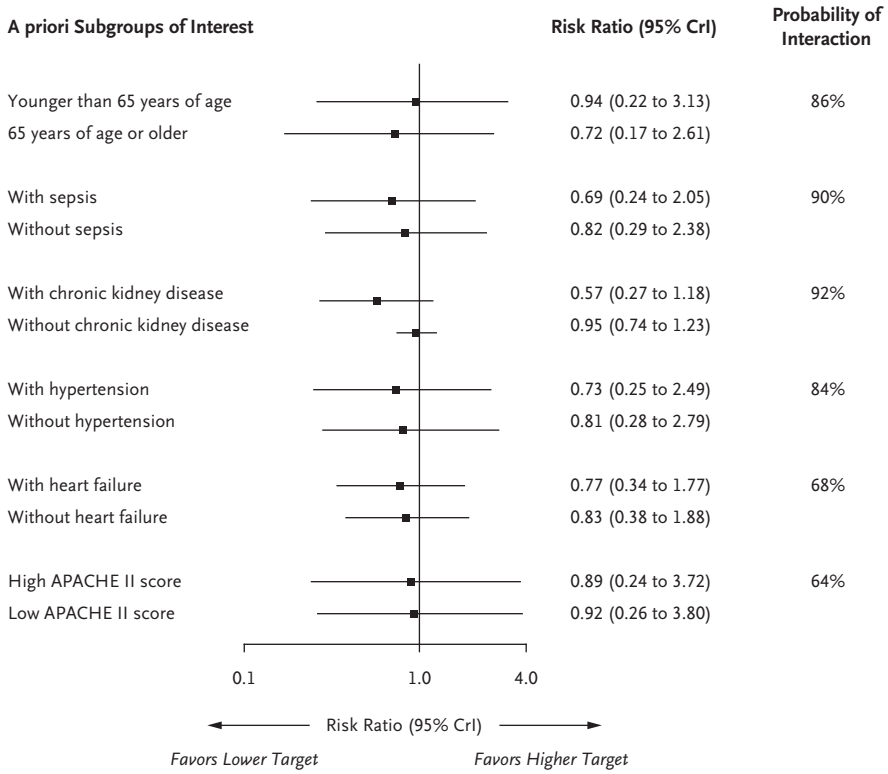

Figure 2. Heterogeneity of Treatment Effect by Subgroups of Interest.*

Acute Physiology and Chronic Health Evaluation II (APACHE II) scores range from 0 to 71 points, with more points indicating increased severity. High APACHE II scores are defined as more than 21 points (based on the sample's median). The APACHE II score was not available for patients included in the SEPSISPAM trial and was derived using a Poisson regression model that was trained in the 65-Trial and OVATION pilot trial subset. These analyses used modified Poisson regression models (because of nonconvergence issues for most analyses with a log-binomial model) with a random intercept for trial and a random effect for treatment allocation. All models included treatment allocation, the average level of the subgroup-defining covariate by trial, the interaction of the average level and treatment allocation, and the individual level covariate with its interaction with treatment allocation. Parameters of interest were the coefficients for treatment allocation and the within-trial interaction. Intervals vary in width because of different modeling specifications and different sample sizes due to missing data for some subgroup-defining covariates (i.e., hypertension data missing for 11.6% of patients; chronic kidney disease data missing for 0.5% of patients; APACHE II scores missing for 0.3% of patients; and age data missing for 0.03% of patients). We used a complete-case analysis. *CrI denotes credible interval.

and the vasopressor strategy associated with the greatest chance of survival.

The strengths of this analysis include the following four points: access to comprehensive individual patient data from published clinical trials addressing the question of vasopressor dosing for critically ill adult patients with vasodilatory shock, primary trials that were conducted across over 100 centers from three different countries and included a wide range of intensive care unit populations, the robustness of the estimates across a range of analyses, and the use of conservative methods (e.g., reliance on a random rather than a fixed effects model[39] and a threshold of 99% for the posterior probability rather than 90% for determining the presence of heterogeneous treatment effects[40]) to reduce the risk of a type 1 error.[41] Our results are largely concordant with a recent study-level meta-analysis including randomized trials of a broad population of critically ill and postoperative patients.[42]

Conversely, several limitations need to be considered. Overall, the current sample size may not be sufficient to detect clinically meaningful effects; our results remain imprecise, and the possibility of heterogeneous treatment effects has not been ruled out. The included trials recorded limited data on which to base analyses of heterogeneity of treatment effect, including specific vasopressors used, coexistence of other forms of shock,

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intravenous fluid administration, cardiac function, or hormone and biomarker levels. Importantly, the fact that blood pressure targets evaluated in the included trials differed precludes conclusions regarding a specific mean arterial blood pressure target to guide the use of vasopressors at bedside. To address these issues, additional clinical trials that randomly assign patients along the full range of plausibly safe blood pressure targets will be necessary. Our results are also limited by the variations in the definition of a higher blood pressure target (a defined range in two trials and usual care in the largest trial) and the protocol adherence in the included trials. Although separation between groups in mean arterial blood pressure values and vasopressor doses was clear in each trial, the actual blood pressure was consistently above the protocolized target.[43] In addition to reducing the ability to detect any difference, modest adherence may affect the translation of results into clinical practice, as clinicians may hesitate between prescribing blood pressure targets as they were protocolized or as they were implemented. Future trials should seek to maximize protocol adherence and the evaluation of nonnaïve per-protocol effect estimates.[44] Finally, we did not capture information on secondary outcomes such as supraventricular arrhythmias or renal failure. Although these secondary end points may bear on clinical decisions, they are less patient centered and more prone to data missingness and outcome ascertainment bias in unblinded trials.

In conclusion, we estimated there is an 87% probability that 90-day all-cause mortality was reduced when a lower mean arterial blood pressure target was used (compared with a higher target) to guide vasopressor therapy for critically ill adult patients with vasodilatory shock. However, the certainty of evidence is low, and this analysis does not exclude the possibility that lower targets may cause harm overall, or in specific subgroups of patients.

Disclosures

Author disclosures and other supplementary materials are available at evidence.nejm.org.

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